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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/286,189	08/05/94	SANHUEZA	S	MISMS1038348

HM12/0927

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EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1648	23

DATE MAILED: 09/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/286,189	Sanhueza et al.
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

☒ Responsive to communication(s) filed on *18 Jun 1997* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-9, and 11-16* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-9, and 11-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Continued Prosecution Application

1. The request filed on 18 June, 1999, for a Continued Prosecution Application (CPA) under 37 C.F.R. § 1.53(d) based on parent Application No. 08/286,189 is acceptable and a CPA has been established.

Status of the Claims

2. Claims 1, 3-9, and 11-16 are pending in the instant application.

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-9, and 11-16 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward RSV vaccine compositions that are capable of inducing non-immunopotentiating and protective immune responses in humans, their methods of preparation, and immunization methods employing said vaccine compositions. The disclosure describes the preparation of a putative vaccine composition comprising purified and inactivated respiratory syncytial viruses (RSVs) of the subtype A (e.g., Long and A2 strains). Virus was prepared from infected

vaccine quality VERO cells, concentrated by ultracentrifugation, purified by sucrose density gradient centrifugation, gel filtration, and chromatography, and inactivated by n-octyl-β-D-glucopyranoside treatment. These compositions were used to immunize cotton rats and their immunogenicity and pathogenicity examined. It was concluded by applicants (see p. 19) that inactivated RSV preparations elicited protective immune responses in the cotton rat without causing the exacerbated pulmonary pathology associated with other putative vaccine compositions.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: 1) The disclosure fails to provide sufficient guidance pertaining to the correlates and determinants of protective immunity. In order to develop an efficacious human RSV vaccine the skilled artisan would require a knowledge of those immune responses (i.e., humoral, cell-mediated, or both) that are critical for conferring protection against viral infection. The skilled artisan would also require a knowledge of the determinants modulating such immune responses so the proper immunogenic compositions can be prepared. However, the art teaches that correlates and determinants of human

protection remain to be elucidated (Hall *et al.*, 1994; Toms, 1995). As Hall and colleagues note (see p. 1394, left col., second paragraph), important hurdles remain pertaining to the development of an efficacious vaccine, the most important of which appears to be "the uncertainty about which components would constitute the ideal vaccine-live virus, attenuated virus, or purified viral proteins?" The authors further emphasize (see p. 1394, middle col., first paragraph) that "We do not even know what type of immune response would be safe and protective in young infants." Toms also points out (see p. 1, first paragraph) that "Neither formalin inactivated nor live virus vaccines, administered intramuscularly, provided significant protection of infants and both have been associated with enhanced rather than reduced severity of disease on subsequent natural infection." However, it is noted that the disclosure fails to teach which RSV antigens and immunogenic compositions (i.e., live virus, inactivated virus, or subunit) confer protective and non-immunopotentiating immune responses.

2) The disclosure fails to provide a sufficient number of working embodiments. It is noted that applicants have administered their vaccine compositions to cotton rats. However, the claims encompass vaccine compositions, their methods of preparation, and methods of immunization employing said compositions, that confer protective and non-immunopotentiating responses in humans. Since the skilled artisan cannot make direct extrapolations, as it pertains to the immunoprotective and immunopotentiating nature of any given putative vaccine composition, between human and cotton rat animal systems (see point three below), the examples provided in the specification do not constitute proper working examples.

3) The disclosure fails to provide data from an art-recognized animal model. The art teaches that a suitable RSV vaccine animal model that enables the direct extrapolation of results obtained

from *in vivo* studies to the clinic has not been developed (Hall, 1994; Toms, 1995; Murphy *et al.*, 1994). Hall concludes (see p. 1394, middle col., first paragraph) that "Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration." Murphy and colleagues question the utility of the cotton rat model and note (see pp. 16 and 17, bridging paragraph) that "the extent of RSV replication in cotton rats is much less than that in humans, and, consequently, the magnitude of immunopathological reactions would be expected to be more limited in scope". The authors also reported (see p. 17, first and second paragraphs) that immunogenic compositions with favorable characteristics in murine systems often fail in primate systems because of reduced immunogenicity, among other factors. Toms also adds (see p. 2, right col., last paragraph) that the "Protection of animals in the laboratory is much more easily achieved than protection of infants against natural infection." Thus, the skilled artisan, upon perusal of the art, would reasonably conclude that the cotton rat model does not represent a reasonable system for assessing the efficacy of a putative human RSV vaccine.

4) The art teaches that the development of efficacious human RSV vaccines is a difficult undertaking and has largely been unsuccessful to date (Salkind and Roberts, 1992; Tristam *et al.*, 1993; Hall, 1994; Murphy *et al.*, 1994; Toms, 1995). A number of factors have contributed to vaccine failure including, *inter alia*, a lack of understanding of the correlates of human protection, antibody-mediated immune suppression in pediatric populations, the requirement for multiple immunizations, the quasispecies nature of RSV thereby necessitating broadly protective compositions, a lack of understanding of the mechanisms responsible for the pathological immunopotentiating effects observed with earlier vaccine

candidates, and the lack of a suitable animal model. The disclosure is silent pertaining to many of these considerations. Salkind and colleague appropriately add (see p. 521) that "Despite intensive efforts, an effective vaccine for RSV has not been developed. The proper components of the vaccine have not been defined but should probably include both RSV subgroups or shared determinants, and the components should induce serological, cellular, and especially mucosal immunity." Accordingly, when all of the aforementioned factors have been considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicants traversal in the Appeal Brief submitted 12 March, 1999, is noted. Applicants assert that the cotton rat model is an art-accepted animal model whose findings can be correlated directly to that in the clinic. Specifically, it was argued that applicants have provided an immunogen that induces titers of neutralizing antibody responses in the cotton rat model that appear to correlate with those observed in resistant infants containing passively acquired maternal serum neutralizing antibody responses. Applicants are directed toward the teachings of Murphy et al. (1994) who clearly reported (see pp. 17, 21, and 22) that many immunogenic compositions in murine models fail to display the requisite immunogenicity in chimpanzees and humans. Thus, the observation that a certain titer of neutralizing antisera has been achieved *in vivo* in the cotton rat would not necessarily lead the skilled artisan to conclude that similar responses could be obtained in the clinic. Considerable genotypic differences exist between murine and primate hosts that influence, in an unpredictable manner, antigen processing and presentation. This is consistent with the evidence provided by Murphy and colleagues who note that several candidate vaccine compositions that induced high titers of neutralizing antibodies in murine systems did not display

directing the claim language toward immunogenic compositions of a non-protective nature, where appropriately supported by the disclosure. However, applicants are advised that any claim amendments may necessitate that application of prior art pursuant to 35 U.S.C. §§ 102 and 103.

Correspondence

5. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

6. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Anthony Caputa, Ph.D., or Laurie Scheiner, can be reached at (703) 308-3995 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 September, 1999